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Mechanisms Counteracting Swelling in Brain Cells During Hyponatremia

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Abstract

Water gain in the brain consequent to hyponatremia is counteracted by mechanisms that initially include a compensatory displacement of liquid from the interstitial space to cerebrospinal fluid and systemic circulation and subsequently an active reduction in cell water accomplished by extrusion of intracellular osmolytes to reach osmotic equilibrium. Potassium (K^+), chloride (Cl^-), amino acids, polyalcohols, and methylamines all contribute to volume regulation, with a major contribution of ions at the early phase and of organic osmolytes at the late phase of the regulatory process. Experimental models *in vitro* show that osmolyte fluxes occur via leak pathways for organic osmolytes and separate channels for Cl^- and K^+. Osmotransduction signaling cascades for Cl^- and taurine efflux pathways involve tyrosine kinases and phosphoinositide kinases, while Ca^{2+} and serine-threonine kinases modulate K^+ pathways. In-depth knowledge of the cellular and molecular adaptive mechanisms of brain cells during hyponatremia contributes to a better understanding of the associated complications, including the risks of inappropriate correction of the hyponatremic condition.

Keywords: volume regulation, taurine, hyposmolarity, regulatory volume decrease

Introduction

The ability to regulate cell volume is an ancient conserved trait present in essentially all species throughout evolution. Maintenance of constant cell volume is a homeostatic imperative in animal cells. Changes in cell water content by affecting the concentration of messenger molecules impair the complex signaling network crucial for cell functioning and intercellular communication. Although under physiologic conditions extracellular fluids have a highly controlled osmolarity, a variety of diseases is paralleled by alterations of systemic osmolarity. In addition, the intracellular volume constancy is continuously compromised by the generation of local and transient osmotic microgradients associated with uptake of nutrients, secretion, cytoskeletal remodeling, and transynaptic ionic gradients.

Cell volume disturbances have particularly dramatic consequences in the brain. The limits to expansion imposed by the rigid skull give narrow margins for buffering of intracranial volume changes. As expansion occurs, constraining of small vessels generates episodes of anoxia ischemia, infarct, excitotoxicity, and neuronal death. Under extreme conditions, caudal herniation of the brain parenchyma through the foramen magnum affects brain stem nuclei, resulting in death by respiratory and cardiac arrest (1).

Hyponatremia is the most common cause of hyposmotic swelling in brain cells. This condition results from an imbalance between intake and excretion of water and electrolytes derived from either an excess of water or a sodium (Na^+) deficit. Water excess may derive from excessive oral intake as in psychotic polydipsia, or more commonly from impaired renal elimination as a consequence of inappropriate secretion of antidiuretic hormone, glucocorticoid deficiency, hypothyroidism, use of thiazide diuretics, and renal or hepatic failure. A variety of diseases or conditions such as head trauma, brain tumor, and cerebrovascular accidents result in hyponatremia associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or the cerebral salt-wasting syndrome (CSWS). Both syndromes have marked similarities with regard to clinical context and presentation, with euvolemia in SIADH and hypovolemia in CSWS the most clear contrasting variables. CSWS is characterized by excessive renal sodium loss (eventually in relation to a natriuretic factor) resulting in volume depletion and hyponatremia (2). Na^+ loss also results from mineralocorticoid deficiency, nephrotic syndrome, osmotic diuresis, vomiting, or diarrhea. Hyponatremia may also be caused by rapid correction of uremia by excessive hemodialysis and by infusion of hypotonic solutions in the perioperative period. Hyponatremia is a common state in the elderly and during pregnancy (3–5). Fatal hyponatremia-induced cerebral edema has been recently associated with the use of the drug Ecstasy (6).

Adaptive Response of Brain Cells to Hyposmotic Conditions: Studies *in Vivo*

In the face of a decrease in external osmolarity, the brain does not exhibit the behavior predicted for a perfect osmometer. During chronic hyponatremia, only approximately 40% of the expected water gain occurs within the first hours; thereafter, total water content decreases progressively to nearly complete normalization (7). The first adaptive response is a compensatory displacement of liquid from the interstitial space to the cerebrospinal fluid; thereafter, the excess in cerebrospinal fluid enters the systemic circulation. The next

adaptive brain reaction is the extrusion of intracellular solutes, mainly the inorganic ions potassium (K^+) and chloride (Cl^-) and a number of small organic molecules, prominently amino acids with osmotically obligated water. Some loss of Na^+ is also observed in whole brain studies, likely displaced from the extracellular space (8). Studies in animal models of chronic hyponatremia have shown the greatest loss of Na^+ and Cl^- during the first 3 h, while K^+ loss is slower, achieving significance only after this first time period (8). From early studies on this subject, it was evident that the decrease in electrolytes was not sufficient to compensate for the loss of water observed and that the involvement of other osmotically active solutes needed to be considered. These molecules, initially referred to as idiogenic osmolytes, were further identified as organic molecules such as amino acids, polyalcohols, and methylamines, which were found to contribute significantly to the adaptive brain response to hyponatremia (8). A decrease in the concentration of myo-inositol, phosphocreatine/creatine, glycerophosphoryl choline and of the most abundant amino acids (glutamate, glutamine, taurine, and glycine) has been consistently observed in chronic hyponatremia (9,10). The contribution of organic osmolytes and electrolytes to the total brain osmolarity change has been estimated as 23–29% and 62–70%, respectively (table 1). While decreases of electrolytes reverse with time, decreases of organic osmolytes, particularly taurine, are sustained as long as hyponatremic conditions persist (9).

Table 1. Electrolytes and organic osmolyte content in rat brain during chronic hyponatremia

Osmolyte (nmol/kg DBW)[a]	Normonatremic	Hyponatremic (nmol/kg DBW)	Decrease
Electrolytes			
Sodium	279	250	29
Potassium	480	424	56
Chloride	152	118	34
All electrolytes	911	792	192
Organic osmolytes			
Glutamate	52.9	32.5	20.4
Glutamine	14.2	6.5	7.7
Taurine	13.8	2.1	11.7
GABA	1.7	0.9	0.8
Aspartate	2.2	1.7	0.5
N-acetylaspartate	7.5	5.9	1.6
Myo-inositol	16	5.3	10.7
Creatine	34.8	17.1	17.7
Phosphoethanolamine	1.2	0.8	0.4
GPC[b]	1.1	0.6	0.5
All organic osmolytes	145.4	73.4	72

a. DBW: dry brain weight. Recalculated from (8,9). Data are from rats after 2–3 days of hyponatremia.
b. GPC: glycerophosphorylcholine.

Taken together, these studies show that immediate response to hyponatremia in brain is in charge of K^+ and Cl^- efflux, and that sustained adaptation is carried out by organic

osmolytes, particularly taurine. This has been confirmed in studies *in vitro* in astrocytes demonstrating how myo-inositol- and taurine swelling-activated efflux persists for several hours after the hyposmotic stimulus, in contrast to glutamate and K^+, which remained unchanged (11,12). These results highlight differences in handling the various osmolytes. Loss of K^+ and Cl^- is an emergency mechanism to counteract brain swelling rapidly, but it is potentially harmful on a long-term basis, in contrast to the relative innocuousness of most organic osmolytes. Taurine in particular may be a perfect osmolyte because it is metabolically inert and exhibits only weak synaptic interaction (13).

Estimation of osmolyte change in all these studies does not discriminate among regional variations within the brain or possible differences in cell type. Studies *in vitro*, in tissue slices as well as in homogeneous cultured cells exposed to media of reduced osmolarity (by decreasing NaCl concentration), represent a suitable initial approach to clarify these questions and to obtain insight into the mechanisms of brain adaptation to hyponatremia. In-depth knowledge of these mechanisms is important to determine the development of symptoms in patients with hyponatremia and is critical for avoiding risks of inadequate correction procedures.

Regulatory Volume Decrease: Cellular and Molecular Mechanisms

Studies in cells such as neurons as well as glial cells in culture have contributed enormously to our knowledge concerning the basic mechanisms of adaptive cell volume recovery after hyposmotic swelling. Cells are, in general, highly permeable to water; therefore, any difference in osmolarity across the membrane results in net water movements in the direction necessary to reach osmotic equilibrium. In the face of a decrease in external osmolarity, cells initially behave as nearly perfect osmometers and swell with a magnitude proportional to the osmolarity reduction. Immediately after, an active volume correction begins, based on the extrusion of intracellular solutes together with osmotically obligated water; this tends to reduce osmotic difference and normalize cell volume. This adaptive mechanism is known as regulatory volume decrease (RVD). The time necessary to fully activate RVD and regain cell volume is variable in the different cell types. In brain cells *in vitro*, RVD occurs rapidly, with a 70–80% recovery reached within a few minutes as a result of osmolyte activation (fig. 1A).

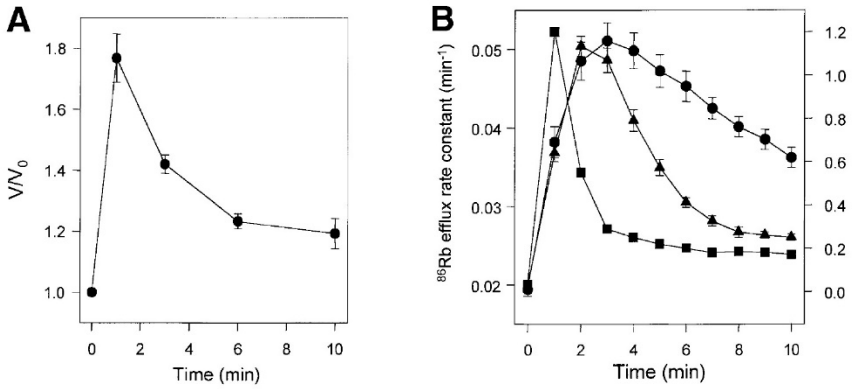

Figure 1. Regulatory volume decrease in cultured cerebellar granule neurons. A. Upon exposure to media of reduced osmolarity (50%), cerebellar granule neurons exhibit a rapid increase in cell volume followed by an active phase of volume regulation occurring despite the persistence of the hyposmotic medium. Volume recovery is approximately 60% within 15 min. B. Volume recovery is accomplished by the efflux of inorganic and organic osmolytes (▲) ^{3}H-taurine (■), ^{125}I (as tracer for Cl^-), and (●) ^{86}Rb (as tracer for K^+). Results are expressed as efflux rate constants, as described in the work of Sánchez-Olea et al. (14,26).

RVD is a complex chain of events requiring a sensor to detect transient changes in cell volume, a signaling cascade to transduce information on volume change into activation of pathways for osmolyte extrusion, and a memory of the original cell volume that sets the timing for inactivation of the regulatory process. During the past years, the majority of efforts have been directed toward identifying and characterizing the osmolyte efflux pathways; thus, it is only recently that interest has been aroused in understanding osmotransduction mechanisms. There is at present only scarce information concerning the nature of volume-sensing mechanisms.

RVD has been studied in detail in astrocytes and neurons from primary cultures (14,15), in neuroblastoma (16), glioma cells lines (17), and in snail neurons (18). RVD has also been found in freshly isolated cells from hippocampus (19). The situation is unclear in more integrated preparations because in some of these preparations RVD has been undetectable (20); nevertheless, the results *in vivo* previously described clearly indicate the occurrence of compensatory mechanisms, although variations in ability to regulate volume may occur within brain regions.

Pathways for Osmolyte Fluxes Activated during RVD

The osmolytes responsible for RVD are essentially the same in most cell types including brain cells and are grouped into two broad categories: the most concentrated intracellular ions (K^+ and Cl^-) and small organic molecules, prominently amino acids, polyalcohols, sugars, and methylamines. In most cells examined to date, osmolyte fluxes occur essentially

by diffusive pathways, i.e., K^+ and Cl^- efflux through separate channels with marginal participation of electroneutral cotransporters, and organic osmolytes through leak pathways with no contribution of energy-dependent carriers (21).

Osmosensitive Channels

Volume-sensitive K^+ and Cl^- fluxes in most cell types occur through separate channels that may possess some interdependence but that clearly exhibited a different selectivity. Cl^- channels activated by hyposmotic swelling are typically outward rectifiers with an intermediate unitary conductance of 40–78 pS, inactivating at potentials of +60 mV and above. These channels have been characterized in numerous cell types (22,23). In brain cells, the volume-sensitive Cl^- channel (VSCC) has been studied in astrocytes (24), C6 glioma cells (25), and cerebellar granule neurons (26). The VSCC has high selectivity of anions over cations but exhibits broad anion selectivity, being permeable to the majority of monovalent anions and even to large anions such as gluconate and methansulfonate. Activation of VSCC requires ATP but not its hydrolysis. Typical Cl^- channel blockers such as DIDS, SITS, 9-AC, and DPC inhibit VSCC with different potencies according to cell type. Other agents with inhibitory effects on the VSCC include NPPB, DDF, niflumic acid, and flufenamic acid (23,24). Notably, arachidonic acid and other polyunsaturated fatty acids are potent VSCC blockers (27,28). For details on the basic properties of VSCC, readers are referred to recent reviews on this topic (22,23).

The molecular species of VSCC are as yet unidentified. Approximately eight members of a family of voltage-gated Cl^- channels have been cloned and characterized. Some are activated by swelling (29), but none unequivocally corresponds to VSCC. Some evidence appears to support the ClC3 channel gene as encoding the channel protein responsible for the volume-sensitive Cl^- current (30), but recent evidence argues against this channel being indeed the VSCC (31). Some molecules with Cl^- permeability properties, namely Icln and the P-glycoprotein, are suggested to play a role in osmosensitive Cl transport either as a Cl^- pathway properly, a possibility recently questioned, or as regulating elements of the functional Cl^- channels (review in Reference 30). Not unlikely but at present undefined is the question of whether different types of VSCC and other anion-permeating molecules coincide in the same cell. An interesting avenue for future research may be the identification of the factors and situations that determine the functioning of one or another of these different osmosensitive channels.

In contrast to the broad similarities found for VSCC in different types of cells, swelling activates at least two different types of K^+ channels. In some—mainly epithelial—cells, volume-sensitive K^+ channels (VSKC) are calcium (Ca^{2+})-dependent, large-conductance (100–200 pS) channels. In other cell types, VSCK channels are small channels with conductances of 20–30 pS, the majority Ca^{2+}-independent (review in Reference 32). While the first group of channels has been clearly identified as high conductance K^+ channels, the identity of the second group is still unclear. Some types of voltage-gated K^+ channels appear to permeate K^+ efflux during RVD in lymphocytes, and Kv channels are activated by hyposmolarity in hippocampal pyramidal neurons, although not all Kv subtypes are responsive (32).

Volume-Sensitive Pathways for Organic Osmolytes

A number of organic osmolytes are released during hyposmotic swelling, but the details of their efflux pathways are known for only a few. The best-characterized organic osmolytes are those for taurine and myo-inositol (33–35); additionally, there is some information on N-acetyl aspartate and ascorbate (36,37). In general, these are bidirectional leak pathways with net solute movement depending on concentration gradient direction. Remarkably, organic osmolyte pathways commonly exhibit a pharmacologic profile similar to that of the VSCC, suggestive of a common pathway with Cl^- or of a close connection between the two pathways (21,35). Other amino acids also responsive to swelling are glycine, GABA, glutamate, and aspartate, which contribute to correction of osmotic disturbance (38). However, this may create additional risks of excitability imbalance, due to their prominent role as synaptic transmitters, to be discussed later. There is recent evidence on hyposmolarity-induced glutamate release insensitive to Cl^- channel blockers, at clear variance with other organic osmolytes (39). This is suggestive of either different pathways or different stimuli and mechanisms for release of this particular amino acid.

Volume Sensor and Osmotransductive Signaling

How cells sense volume changes is the initial and critical step in the chain of reactions activated for volume correction, yet this has remained elusive to date. Among possible mechanisms considered to play this role are membrane receptors such as integrins or receptors with intrinsic tyrosine kinase activity, cytoskeleton rearrangements, dilution of cytosolic macromolecules, decrease in intracellular ionic strength, stretch-induced activation of adhesion molecules, activation of phospholipases, or changes in the concentration of signaling molecules such as Ca^{2+} or magnesium (Mg^{2+}) (fig. 2). Although to date none of these possesses sufficient supporting experimental evidence, this is at present a very active field of research (40). The question of volume sensing is also closely related to mechanisms of osmolyte flux inactivation. At present, this is an essentially unexplored aspect of RVD.

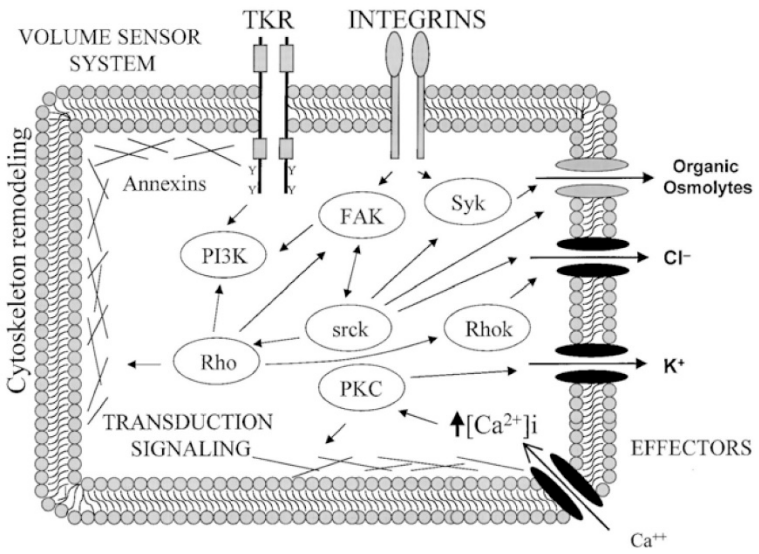

Figure 2. Hypothetical scheme of the elements of volume sensing, osmotransduction, and activation of osmolyte pathways. The volume sensor system includes membrane and submembrane elements such as integrins, membrane receptors with intrinsic tyrosine kinase activity (TKR), annexins, and cortical actin cytoskeleton remodeling. Osmotransduction signaling includes Ca^{2+} and a number of protein tyrosine kinases, including focal adhesion kinase (FAK), SYK, src-related kinases (srck), the tyrosine-kinase-activated kinase phosphoinositide-3 kinase (PI3K), and protein kinase C (PKC). The small GTPase Rho and its kinase RhoK may also act as osmosignaling elements. Not all enzymes appear involved in the same cell type.

Calcium and protein kinases are among the most likely candidates to act as osmotransductory elements. One of the most constant features of hyposmotic swelling is an increase in cystolic Ca^{2+} (32) (fig. 2). Despite this, the main corrective osmolyte efflux pathways and consequently RVD are Ca^{2+}-independent in a large variety of cell types. This is the case for brain cells, in which VSCC, VSKC, and organic efflux pathways are largely Ca^{2+}-independent (32). The more commonly accepted interpretation of these results is that cytosolic Ca^{2+} increase is an epiphenomenon resulting from activation by swelling of Ca^{2+} influx pathways and/or of release mechanisms from intracellular stores (41), but that this increase is not part of the osmosignaling cascades. In cells such as epithelial cells, the magnitude of hyposmolarity-evoked cytosolic Ca^{2+} elevation is sufficient to activate Ca^{2+}-dependent large conductance K^+ channels, which once activated, predominantly contribute to RVD. As a consequence, RVD is Ca^{2+}-dependent in these cells (32).

Protein kinases of different types modulate some osmolyte pathways. In contrast to the constancy of the cytosolic Ca^{2+} elevation, the effect of protein kinases appears to be cell-specific. Protein kinase C (PKC) appears involved in the function of the VSCC but with different effects (activation or inhibition) according to cell type (22). Protein kinase A does not influence RVD in most cells but may be involved in the modulatory action of hormones and other factors on cell volume regulation. Protein tyrosine kinases (PTK) have recently

received special attention as elements of the osmotransduction cascades as a result of the potent effect of blockers of PTK reducing the osmosensitive efflux of Cl^- and taurine (42,43). This effect has been reported in cultured astrocytes and neurons and in more integrated preparations such as the supraoptic nucleus and hippocampal slices (34,39). *In vivo*, PTK appear related to swelling-evoked amino acid release in heart Langendorff preparations (44). Furthermore, in cultured cells inhibition of tyrosine phosphatases, which prolong the protein phosphorylation reaction, increases osmolyte fluxes (42) (fig. 2). A modulatory role of PTK on volume-sensitive K^+ channels has not been reported but Ca^{2+} and PKC are involved in VSKC in some cell types, as previously mentioned (fig. 2).

The site within the complex signaling network modulated by PTK has not been identified. A possible target is the phosphoinositide kinase PI3K, a tyrosine-kinase-activated kinase, because inhibition of this enzyme has a marked influence in reducing the volume-corrective fluxes of Cl^- and taurine (42,43). PI3K is a key element in signaling cascades with links to tyrosine-kinase membrane receptors and the integrin-FAK pathway. PI3K also relates to small GTP-ases of the Rho family that in turn modulate the dynamics of the cytoskeleton (45) (fig. 2).

A role for phospholipases in osmotransduction, in particular the cPLA2 form, is suggested by reports in neuroblastoma and in Ehrlich ascites cells, showing a strong correlation between arachidonic acid release and volume-sensitive taurine efflux, which are blunted by blockers of this specific enzyme (46).

Isovolumetric Regulation

The experimental model of abrupt and large reduction in external osmolarity has contributed importantly to our knowledge concerning the mechanisms by which cells face osmotic challenges. However, this model does not closely reproduce the conditions *in vivo*. Even in acute hyponatremia, changes in external osmolarity never exceed –16% and onset of hyposmolarity appears gradually. A better paradigm for approaching these conditions was developed by Lohr and Grantham (47) in renal tubule cells exposed to small and gradual changes in osmolarity. Under these conditions, cells do not swell even if external osmolarity is drastically decreased. This constancy in cell volume is not due to swelling being restricted, but is rather due to rapid and efficient correction of the continuous change in water content. This volume adjustment, similar to models of abrupt hyposmotic shock, appears to be accomplished by active extrusion of intracellular osmolytes (48). Molecules involved and mechanisms in operation are not known in detail, as studies on isovolumetric regulation (IVR) are still scarce. Occurrence of IVR has been found in only two types of renal cells (47,49), in hippocampal slices (50) (fig. 3), and with lower efficiency in C6 glioma cells (51) and in cardiomyocytes (52). In A6 cells and in myocytes, IVR stimulates K^+ release, but only at delayed phase of IVR, with an efflux threshold at –30% hyposmotic external osmolarity. In contrast, amino acids, particularly taurine, appear involved at earlier phases of volume regulation, showing efflux thresholds at approximately –10 to 12% hyposmolarity (50) (fig. 3). There is no information on osmotransduction factors or signaling messengers involved in this model of volume regulation, and possible similarities or dissimilarities of this mechanism of volume control in different cell types have not been explored to date. This is an interesting avenue of research because as previously mentioned,

this experimental model approaches physiologic and pathologic situations generating changes in cell volume in brain.

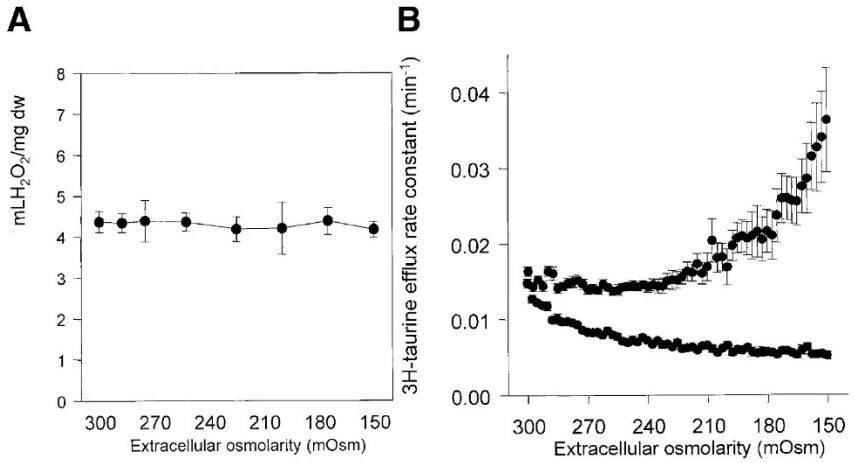

Figure 3. Isovolumetric regulation in hippocampal slices. A. Slice water content remains unchanged when slices are exposed to small and gradual changes in osmolarity (1.8 mosm/min). B. Constancy in cell volume is an active process accomplished by the efflux of osmolytes, as illustrated for taurine efflux. Details of experiments are described according to Franco et al. (49).

Hyponatremia and Hyperexcitability

A serious clinical consequence of acute and severe hyponatremia is the generation of epileptiform activity and increased susceptibility to seizures (53). In studies in hippocampal slices, osmolarity reduction causes an increase in amplitude of evoked field potentials and of excitatory postsynaptic potentials, which is inversely related to osmolarity (54). Hyposmolarity does not affect cell properties such as resting membrane potential, cell input resistance, and action potential threshold and duration (55). The manner in which osmolarity alters synaptic transmission is not fully understood. It may result from either hyperfunction of excitatory synapses and/or from nonsynaptic mechanisms derived from reductions in the size of the extracellular space. The increase in excitatory synaptic activity may be the consequence of the well-documented, swelling-activated glutamate release (39,55). On the other hand, narrowing of the extracellular space due to cell swelling may also be a source of hyperexcitability, either by enhancing ephaptic interactions and/or because increase of extracellular K^+ concentration and reduced diffusion of neurotransmitters prolong the synaptic function (53,56). These possibilities, which do not exclude each other, may all contribute to generate hyposmotic-associated hyperexcitability. In support of this interpretation, the Cl^- channel blocker furosemide prevents extracellular space reduction and blocks epileptiform activity in a variety of *in vitro* models (57). Furosemide prevents the kainic acid-induced, synchronized burst discharges in hippocampal slices (57).

Differences in Brain Cell Swelling in Hyponatremia

Cultured brain cells exposed to hyposmolarity reductions exhibit an immediate and general increase in cell swelling. However, this homogeneity has not been observed in more integrated preparations, in which the response of individual neurons to lowering osmolarity varies greatly. In pyramidal cells freshly isolated from CA1 region of the hippocampus, at least three different populations of cells could be identified according to their response to decreasing osmolarity. One group of cells swells immediately, while other groups exhibit a delayed response or are resistant to swelling (19). Differences are also observed between hippocampal regions in which CA1 and the dentate gyrus swell more than CA3 (58). Within the same region, as in CA1, the stratum radiatum and the stratum oriens containing the apical and basal dendrites, respectively, are notably more responsive to hyposmotic swelling than the stratum pyramidale, formed by the cell somata (58). The reason for these differences is unclear to date. Lack of swelling in some cells or regions may result from (i) an intrinsic mechanism preventing water entry such as reduced expression of aquaporins, (ii) activation of highly efficient processes of volume adjustment, or (iii) temporary redistribution of osmolytes to nearby cell compartments. In this respect, an elegant *in vivo* study by Nagelhus and co-workers (59) in cerebellum of water-loaded rats shows an immediate redistribution of taurine-cell content in Purkinje cells to nearby glial elements in response to the hyposmotic condition. As a result, astrocytes swell while neurons are spared (fig. 4).

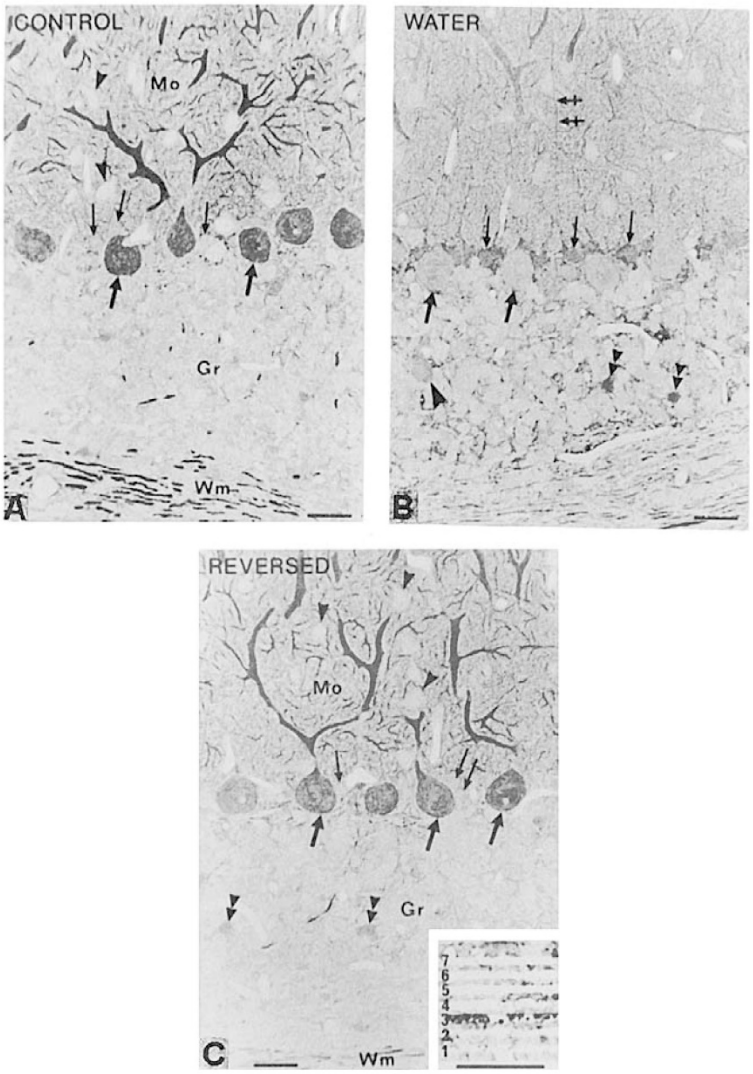

Figure 4. Redistribution of taurine-like immunoreactivity in rat cerebellar cortex following water loading. Details of the experiment are as in Reference 58. Photomicrographs of pairs of neighboring semi-thin sections treated with taurine antiserum are as described in Reference 58. Animals were treated with isotonic saline (A) or water (B) 4 h prior to killing, or with water followed by hypertonic saline (C). The figure shows the highly concentrated taurine in Purkinje cells (large arrows), which upon water load is transferred to the adjacent glial elements (arrows). The original distribution is restored after hyposmolarity correction. Double arrowheads represent different types of cells labeled with taurine. This is part of figure 2 from the work by Nagelhus et al. (58), reproduced with permission.

Risks of Rapid Correction of Hyponatremia

Acute, severe hyponatremia (Na^+ serum concentration <115 mM) produces clear symptoms of neurologic damage due to brain edema, with the consequent increase in intracranial pressure. The commonly used procedure to correct hyponatremia is administration of hypertonic saline solutions. Saline/acetate solutions have also proved highly efficient to correct mild hyponatremia (60). In cases of SIADH, fluid restriction is usually the first line of treatment. It is important to mention in this respect that a clear distinction should be made between a diagnosis of SIADH and of CSWS, which as mentioned previously may have similar symptoms. While fluid restriction is appropriate to correct hyponatremia associated with SIADH, it is detrimental to patients with CSWS and can even be lethal (2,61). An increase in plasma Na^+ concentration of approximately 10–15 mmol/L is normally sufficient to prevent permanent brain damage in severe, acute hyponatremia. It is currently accepted that the rate of correction of acute hyponatremia should be no more than 0.5 mmol/L/h and should be interrupted when serum Na^+ levels have increased to 125–130 mmol/L (62). These precautions are necessary because overly excessive and rapid corrective procedures may result in brain injury, likely due to the adaptive mechanisms developed to counteract hyponatremia described in this review. As a consequence of these adjustments, solute intracellular pools change their concentration to attain an osmotic balance with the external modified condition, i.e., the osmolarity of the cytosol is in equilibrium with an external hyposmotic environment. When the increase in plasma tonicity that accompanies correction of chronic hyponatremia restores the normal isosmotic condition, this condition is now sensed as hyperosmotic by brain cells, which consequently dehydrate until new adaptive mechanisms are activated. The main risk of this situation is a neurologic sequel of demyelinating lesions in the brain, a pathology known as osmotic demyelination syndrome (8). This pathologic entity is characterized by a symmetric focus prominently in the basis pontis, but extrapontine demyelinating lesions have also been found in the basal ganglia, internal capsule, lateral geniculate body, and cortex (63). The salient clinical features of the syndrome include motor abnormalities progressing to flaccid quadriplegia, occasional respiratory paralysis, mental state disturbances, lethargy, and coma. Why demyelination develops is not well understood. Recent studies have focused on a disruption of the brain blood barrier as the gating factor of the degenerative process (64,65). The current hypothesis is that disruption of the tight junctions of the blood brain barrier as a consequence of brain dehydration might expose oligodendrocytes to substances normally excluded from the brain, such as complement, which could be the precipitous factor of demyelination. Situations predisposing to the development of the demyelination syndrome associate with preexisting conditions such as alcoholism and malnutrition (8). Particular care should be taken in correcting hyponatremia in patients with an associated clinical condition of hypoxia. Studies in animals as well as in humans (66–68) have shown that hypoxia combined with hyponatremia produces a major increase in brain edema, injury, and mortality. This is possibly a consequence of inefficiency of the compensatory mechanisms of cell volume regulation due to intracellular Na^+ increase and subsequent Cl^- influx occurring in the hypoxic condition as a result of the energetic failure (69).

Conclusions

Knowledge concerning the cellular and molecular mechanisms subserving brain adaptation to hyponatremia has notably progressed in the last decade. All of this information has contributed to understanding the risk of the pathologic consequences of an inappropriate correction of the hyponatremic patient and to guide the clinicians toward a rational, optimal therapeutic approach.

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